National Essential Medicine List Medication Review Process
Adult Hospital level
Component: Musculoskeletal disorders

Date: 26 November 2015

Medication: Naproxen, meloxicam and piroxicam in arthritis

Introduction:
Inflammatory arthritis results in structural damage to joints, which results in persistent pain in these patients. The management of pain is an important aspect of the management of arthritis. Comorbidities are highly prevalent in this group of patients, so considering the safety of various analgesics with this in mind is important.

Search strategy and article selection:

A search of the Cochrane database identified 1 relevant review (updated 2012). The review assessed the efficacy and safety of pharmacological pain treatment in inflammatory arthritis with gastrointestinal or liver comorbidities, or both. [i]

Meloxicam in arthritis:

1. PubMed: ("Arthritis"[Mesh] AND "meloxicam"[Supplementary Concept]) AND "Treatment Outcome"[Mesh] AND ((Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 17. Two studies rejected: 1 did not match the drug under review, 1 did not match the disease state under review.

2. Google scholar: the following terms were used: 'meloxicam', 'cardiovascular safety', 'gastrointestinal safety' and 'meta analysis'.

3. Bandolier website: the following term was used "meloxicam".
   Results: 1 – "Nabumetone & meloxicam gastrointestinal safety"; that summarized the meta-analysis by Schoenfeld et al (1999).

Naproxen in arthritis:

1. PubMed: "Arthritis"[Mesh] AND "Naproxen"[Mesh] AND ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ((Controlled Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 85. Studies were excluded because: they did not match the drug under review; they compared treatment combinations not under review. Studies that were only available in abstract form were excluded.

2. An article identified from a report on the PRECISION trial identified one further meta-analysis from Lancet that was considered eligible for inclusion in this review[ii]. The

primary vascular outcome was major vascular events (non-fatal myocardial infarctions, non-fatal stroke, or death from a vascular cause). Other vascular outcomes included major coronary events (non-fatal myocardial infarction or death from coronary disease), stroke, and hospitalization for heart failure. The primary gastrointestinal outcome was upper gastrointestinal complications (upper gastrointestinal perforation, obstruction or bleed).

3. Bandolier website: the following term was used "naproxen".
   Results: 2 – "The Oxford League table of analgesic efficacy"; "NSAIDs and adverse effects" and" Myocardial infarction: aspirin, NSAIDs, and COXIBs".

Piroxicam in arthritis:

1. PubMed: ("Arthritis"[Mesh] AND "piroxicam"[Supplementary Concept]) AND "Treatment Outcome"[Mesh] AND ((Clinical Trial[ptyp] OR Multicenter Study[ptyp] OR Randomized Controlled Trial[ptyp]) AND "humans"[MeSH Terms] AND English[lang] AND "adult"[MeSH Terms])
   Results: 18. Studies were excluded as they did not match the medicine or the formulation under review; the comparator medicine was not standard of care; study determined non-pharmacological outcomes or studies compared duration therapy.

2. Google scholar: the following terms were used: 'piroxicam', 'meta-analysis' and 'safety'.

3. Bandolier website: the following term was used "piroxicam".
   Results: 2 – "The Oxford League table of analgesic efficacy"; "NSAIDs and adverse effects".

Comparable doses

Comparative doses were derived from the WHO defined daily doses index[iii]:

Medicine	**WHO ATC DDD**
Meloxicam	15 mg
Naproxen	500 mg
Piroxicam	20 mg
Ibuprofen	1200 mg
Diclofenac	100 mg

Evidence synthesis:

The SELECT[iv] and MELISSA[v] trials, and the study by Yocum *et al*[vi] , were sponsored by Boehringer Ingelheim GmbH, manufacturers of Mobic® (meloxicam). There was no mention of the method of randomization in these trials. These trials indicated adverse events using the Adverse Reaction Terminology List/Coding Thesaurus Of the World Health Organization, although they are presented in different formats in each study. The MELISSA trial had an increased attrition rate with the meloxicam group due to lack of efficacy. The McGettigan study is a systematic review only[vii]. The manufacturer-funded meta-analyses [viii,ix] suggesting a lower risk of gastro-intestinal complications with meloxicam, were of low-quality; as details of the quality and individual results of the included RCTs were not reported.

Effectiveness

1. Naproxen

Compared with oral acetaminophen naproxen had significantly better effect sizes for pain at 3 months (0.20, 95% CI 0.03 to 0.37), in the treatment for osteoarthritis of the knee. However when compared to celecoxib, there was no difference in effect size (0.05, 95% CI -0.08 to 0.17) The Oxford League table of analgesic efficacy[x] shows a NNT of 2.5 for ibuprofen 400 mg compared to a NNT of 2.7 for naproxen 400-550 mg and a NNT of 3.4 for naproxen 200/220 mg.

2. Meloxicam

To date, no RCTs of meloxicam have been included in Cochrane reviews. The double-blinded RCTs that were identified comparing melxicam to other NSAIDs were generally comparable in terms of efficacy, except in 2 RCTs [v, vi] (where attrition was greater in the meloxicam group due to lack of efficacy).

RCT	Study design	Study comparators	Effect	Comments
Hawkey et al (1998) [v] (MELISSA TRIAL)	Double-blnd, randomised, RCT; n=9323, over 28 days.	Meloxicam 7.5mg (n=4635) vs diclofenac 100mg slow release (n=4688) in osteoarthritic patients.	**Efficacy:** - Diclofenac more efficacious than meloxicam (assessed by VAS scale) statistically significant but not clinically significant (differences were small & did not reach pre-determined levels of clinical significance) -Significantly more patients discontinued meloxicam because of lack of efficacy (80/4635 vs 49/4688; p < 0.01). **Safety:** -Fewer GI adverse events with meloxicam(13%) vs. diclofenac (19%; p < 0.001).; with less dyspepsia (p < 0.001), nausea & vomiting (p < 0.05), abdominal pain (p < 0.001) & diarrhoea (p < 0.001). -Patient days of hospitalization was 5 vs 121 for meloxicam vs diclofenac, respectively. 254 patients receiving meloxicam (5.48%) vs 373 (7.96%) on diclofenac (p < 0.001) withdrew from the study due to AEs – GI AEs: 3.02% vs 6.14%; p < 0.001, respectively.	• Attrition was greater in the meloxicam group due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above
Dequeker et al (1998) [iv] (SELECT TRIAL)	Multi-centred, double blind, double-dummy, randomized, parallel gp trial, over 28 days. Intention to treat analysis.	Meloxicam 7.5 mg (n=4320) vs piroxicam 20 mg (n=4336) in osteoarthritic patients.	**Efficacy:** Comparable efficacy assessed on 100 mm VAS: - mean treatment difference (meloxicam vs. piroxicam) at the end of trial was 1.97 mm (95% CI 1.01 to 2.94), NS **Safety:** Adverse events lower in the meloxicam vs. piroxicam group (22.5% vs. 27.9%; p < 0.001), Piroxicam vs meloxicam: - GIT adverse events: 15.4% vs 10.3%; p < 0.001 - nausea/vomiting: 3.4% vs 2.5%: p < 0.05 - abdominal pain: 3.6% vs 2.1%; p <	• 79% of patients in both treatment groups were pre-treated with NSAIDs. • 1.7% in meloxicam vs. 1.6% in piroxicam group withdrew due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 20 mg (meloxicam vs piroxicam) contrary to WHO DDD – see above.

			0.001 - 16 vs 7 perforations, ulcerations or bleeding (PUBs) (RR: 1.4). - 4 vs 0 complicated PUBs (RR:1.9).	
Hosie (1996)[xi]	Multi-centred, double blind, double-dummy, randomized trial, over 6 months. Intent to treat analysis.	Meloxicam 7.5 mg (n=169) vs diclofenac 100 mg slow release (n=167) in osteoarthritic patients	**Efficacy:** Meloxicam showed a greater reduction of overall pain (mm on VAS -28.1 ± 29.4 vs -30.9 ± 29.1), pain on movement (mm on VAS -29.5 ± 31.1 vs 32.8 ± 28.5), greater global efficacy (mm on VAS 35.9±29.1 vs 32.1±27.4) and less duration of stiffness following inactivity (minutes --43± 167 vs -33±62), all NS. NS QoL scores were comparable to diclofenac (-2.3±3.7 vs -2.2±4.2) **Safety:** -Adverse effects reported in 101/169 (59.8%) vs 101/167 (60.5%) of meloxicam vs diclofenac groups, respectively. - More SAEsin diclofenac vs melociam group (22% vs 15.8%) -More patients withdrew due to adverse effects in the diclofenac (22%) vs meloxicam (12.4%) groups.	• 66 patients withdrew due to AEs (n=21, meloxicam; n=31; diclofenac) or lack of efficacy (7 in each group). • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above. • Median dose of concomitant paracetmol was lower in meloxicam vs diclofenac group (185vs 245 mg/day, p-0.0123).
Hosie (1997)[xii] ACCESSED ABSTRACT ONLY	Randomised, double-blind, parallel-group trial, over 6 months.	Meloxicam 15 mg (n=306) vs piroxicam 20 mg (n=149) for proven osteoarthritis of the knee or hip (details of diagnosis not reported in the abstract).	**Efficacy:** - Comparable effectiveness between meloxicam and piroxicam for overall pain, pain on movement, joint stiffness, global efficacy and quality of life (effect sizes not provided in the abstract). **Safety:** -Incidence and type of AEs reported were similar in both study groups -More GIT AEs reported in 24.2% of meloxicam-treated patients vs.30.2% of piroxicam-treated patients.	Details of patients withdrawing from the study not provided for in the publication abstract.
Valat (2001)[xiii]	Multi-centred, double blind, double-dummy, randomized, parallel gp trial, over 14 days. Intention to treat analysis.	Meloxicam 7.5 mg (n=169) vs diclofenac 100 mg slow release (n=167) for osteoarthritis in the lumbar spine.	**Efficacy:** Statistically significant reduction in pain on motion of lumbar spine (assessed on 100 mm VAS) with meloxicam vs. diclofenac after 3 days (mean(SD)): 15 (18) mm vs 17 (21 mm); p <0.05. **Safety:** - GIT adverse events greater with diclofenac vs meloxicam (17.8% vs 12.8%), NS. -Global tolerability was significantly better than diclofenac, assessed by patients (p=0.049) and investigators (p=0.0072).	• 5 patients withdrew due to AEs in meloxicam group vs. 10 in diclofenac group. No withdrawals due to lack of efficacy. • Comparative doses considered to be 7.5 mg vs 100 mg (meloxicam vs diclofenac) contrary to WHO DDD – see above.
Linden (1996)[xiv]	Multi-centred, randomised, double-blind, parallel group trial, over 42 days. Intention to treat analysis.	Meloxicam 30 mg (n=29) evaluated separately and evaluated descriptively but not reported in the publication; and meloxicam 15 mg (n=129) vs piroxicam 20 mg (n=127) in an ITT, for osteoarthritis of the hip.	**Efficacy:** - No significant difference in pain at movement between meloxicam vs piroxicam at 42 days. **Safety:** - More GIT AEs reported with piroxicam vs meloxicam (22.8% vs 20.9%). -Global tolerance (100 mm VAS) was similar in both treatment groups.	• 12 patients withdrew due to AEs in meloxicam group vs. 10 in piroxicam group. Withdrawl due to lack of efficacy was not reported.
Goei(1997)[xv]	Multi-centred, randomised, double-blind trial, over 6 weeks. Intention to treat analysis.	Meloxicam 15 mg (n=128) vs diclofenac 100 mg slow release (n=130) for	**Efficacy:** - Trend seen for efficaciousness, favouring meloxicam (pain on movement, global efficacy and paracetamol consumption), NS.	• 21 patients withdrew due to AEs in meloxicam group vs. 24 in diclofenac group.

		osteoarthritis of the knee. Intention to treat analysis.	**Safety:** - More AEs reported in diclofenac vs. meloxicam groups - 44 (34.4%) vs 47 (36.2%). - Most frequent AEs were GIT: 34(26.2%) vs 21 (16.4%) in the diclofenac vs meloxicam groups, respectively. - 1 patient in the diclofenac group was hospitalized due to a gastric ulcer, at 22 days. - Both drugs were well tolerated when assessed by the patients on a visual analog scale (VAS).	Withdrawl due to lack of efficacy was not reported. - 5/128 patients in meloxicam group vs 3/130 in diclofenac group withdrew, due to lack of efficacy. - Cardiovascular disorders reported were 3% in the meloxicam group vs 1% in the diclofenac group.

The MELISSA trial showed no difference between meloxicam 15 mg and diclofenac 100 mg for pain on active movement (actual difference between treatments mean 2.29, 95% CI 1.38 to 3.20) and pain at rest (1.54, 95% CI0.59 to 2.49)[vi], as assessed with 100 mm visual analogue scale (VAS). There was greater attrition in the meloxicam group due to lack of efficacy – dropout rate was 80/4635 vs. 49/4688; $p < 0.01$ for meloxicam *vs*. diclofenac, respectively (actual difference 0.68%; odds ratio 1.66, 1.16 to 2.38, $p < 0.01$).

3. Piroxicam

A RCT[xvi] showed no difference between diclofenac 100 mg/day (n=32) and sustained-release etodolac 400 mg/day (n=32) for treating osteoarthritis of the knee determined by 100 mm visual analogue scale; whilst another 8-week, multi-centered, double-blind RCT[xvii] showed comparable efficacy between piroxicam and standard formulation etodolac for treating osteoarthritis of the knee and hip with no statistically significant differences in any efficacy assessment at any observation. More adverse events were reported with etodolac vs. piroxicam (30% vs. 46%; $p < 0.01$); whilst the difference in gastrointestinal adverse events (20% vs. 29%) was not significant. Decrease in haemoglobin occurred in 22% of patients, but with no significant difference between the 2 groups.

A meta-analysis[xviii] of RCTs comparing piroxicam to other NSAIDs showed a trend of comparable global efficacy to other NSAIDs (OR 1.06; 95% CI 0.96 to 1.18). Similar results were shown when short-term trials (≤ 4 weeks) and long-term trials were analysed; OR 1.18; 95% CI 0.96 to 1.34 and OR 1.07; 95% CI 0.97 to 1.19, respectively. However, for mobility or stiffness, piroxicam was reported to be significantly more efficacious than indomethacin ($p = 0.04$, but no effect size provided) whilst comparable to other NSAIDs (effect size 0.02; 95% CI -0.14 to 0.18, p=0.82). Piroxicam was also shown to be significantly better in terms of articular swelling vs. other NSAIDs (effect size 0.26; 95% CI 0.07 to 0.44; p=0.008). However, a number of limitations of this meta-analysis cautions of the reliability of the results. Search terms were not provided; details of the RCTs were not described; RCTs with all indications for NSAIDs were included; results of quality assessment of RCTs using Jadad score were not provided and the pooled results of global efficacy and safety was from clinically heterogeneous RCTs (differs in population and outcomes).

Safety considerations

1. Naproxen

Cardiovascular effects

Trelle *et al* found no association between naproxen and myocardial infarction compared with placebo (rate ratio 0.82, 95% CI 0.37 to 1.67)[xix]. However, in their secondary outcomes of stroke, cardiovascular death, and death from any cause, naproxen was associated with increased incidence of stroke (1.76, 95% CI 0.91 to 3.33). Cardiovascular death (0.98, 95% CI 0.41 to 2.37) and death from any cause (1.23, 95% CI 0.71 to 2.12) was not associated with naproxen use.

In the Lancet meta-analysis, naproxen was not associated with significant risk of major vascular events (rate ratio 0.93, 95% CI 0.69 to 1.27; p=0.66)[ii]. There was no increase in major coronary events (0.84, 95% CI 0.52 to 1.35, p=0.48). There was no evidence for increased risk of stroke (0.97, 95% CI 0.59 to 1.60, p=0.90). There was increased risk of hospitalization due to heart failure with naproxen (1.87, 95% CI 1.10 to 3.16, p=0.0197). There was no risk of vascular death associated with naproxen (1.08, 95% CI 0.48 to 2.47, p=0.80).

A systematic review of population-based controlled observational studies by McGettigan *et al* showed a relative risk of 1.09, 95% CI 1.02 to 1.16 for pooled cardiovascular risk[viii]. Different doses of naproxen do not appear to affect its safety on cardiovascular outcomes.

Gastrointestinal effects

The Lancet meta-analysis showed increased risk of upper gastrointestinal bleed associated with naproxen compared to placebo (4.22, 95% CI 2.71 to 6.56, p<0.0001)[ii]. [There was an association with increased incidence of upper gastric bleeds within the first 6 months with naproxen (6.31, 95% CI 3.81 to 10.44).

2. Meloxicam

Cardiovascular effects

The pooled cardiovascular effects of meloxicam by McGettigan *et al* showed a pooled RR 1.20, 95% CI 1.07 to 1.33; p=0.7, I^2=0 against meloxicam's favour[vii]. The data on meloxicam is, however, relatively sparse. The meta-analysis of observational studies showed that of the NSAIDs, meloxicam was associated with the 3rd highest risk, after diclofenac and indomethacin, but was comparable to ibuprofen (RR 1.18, 95% CI 1.11 to 1.25, p<0.0001, I^2=81.90).

Pooled analysis of data from 28 trials[xx] showed a similar risk of thromboembolic events for meloxicam, at either dose (0.2%), compared to piroxicam (0.1%) and naproxen (0.0%), but a lower risk to that observed with diclofenac (0.8%). Limitations in this analysis include the short duration of included RCTs (< 60 days) and the pooling of source data eliminating the effect of randomisation.

Gastrointestinal effects

MELISSA[v] showed an increased incidence of gastrointestinal disorders with diclofenac (18.71%) compared to meloxicam (13.31%), p<0.001; difference of 5.4% favouring meloxicam. There was no difference between groups regarding incidence of perforations, ulcerations, or bleeding (PUBs). Yocum *et al*[xxi] showed increased gastrointestinal adverse event rates for diclofenac (30%) compared with meloxicam (3.75mg and 7.5mg, 21%; 15mg 18%), at 12 weeks treatment; absolute risk reduction of 9% when comparing meloxicam 7,5 mg to diclofenac 100 mg;

increasing to 12% for meloxicam 15 mg compared to diclofenac 100 mg. Attrition rate was similar between all groups.

SELECT[iv] showed a decreased incidence of gastrointestinal adverse events with meloxicam 7.5mg daily compared with piroxicam 20mg daily (10.3% vs 15.4%, $p < 0.001$; actual difference of 5.1% favouring meloxicam).

Pooled analysis of data from 28 meloxicam trials[xx] showed a 0.03% risk of upper gastrointestinal events for meloxicam 7.5 mg compared to diclofenac 100-150 mg, naproxen 1 g and piroxicam 20 mg, $p<0.02$. The risk increased to 0.2% for meloxicam 15 mg compared to piroxicam 20 mg, $p < 0.03$. The study suggests that the risk of serious gastrointestinal complications was generally lower than other NSAIDs but is dose dependant. However, limitations of this analysis included the short duration of included studies (< 60 days) and the poorly defined definition of gastrointestinal events that was heterogenous across studies.

3. Piroxicam

Cardiovascular effects

McGettigan *et al's* meta-analysis of observational studies[vii] for cardiovascular risk showed that piroxicam was not associated with increased risk (RR 1.08, 95% CI 0.91, 1.30, p=0.3, I^2=18.9%), and was comparable to cardiovascular risk associated with naproxen (RR 1.09, 95% CI 1.02 to 1.16, $p <0.0001$, I2 = 70.7%). However, cardiovascular risk rate for piroxicam was not statistically significant and studies were heterogenous.

Gastrointestinal effect

Pooled analysis of data from 28 meloxicam trials[xx] showed that piroxicam compared to placebo, was associated with an increased risk of gastrointestinal complications (RR 1.66; 95% CI 1.14, p=2.44), similar to that of naproxen (RR 1.83; 95% CI 1.25, p=2.68), whilst meloxicam (RR 1.24; 95% CI 0.98, p=1.56) and ibuprofen had a lower risk (RR 1.19; 95% CI 0.93, p=1.54). Limitations of this analysis have been described above. However, study of case-controls[xxii] showed that piroxicam had a higher risk for hospitalization of upper gastrointestinal bleed when compared to non-NSAID use than naproxen (RR 13, 95% CI 7.8 to -20 vs RR 7.3, 95%CI 4.7 to 11; risk difference of 6.65%).

Dermatological effect

The US FDA spontaneous adverse events reporting system found an association of Stevens-Johnson syndrome and toxic epidermal necrolysis with NSAIDs (particularly piroxicam and tenoxicam – relative risk of 34). However, the estimated incidence is low - 1 per 100 000 patients during the 1st 8 weeks of therapy[xxiii, xxiv].

Evidence quality:

Studies of meloxicam in arthritis are relatively scarce. In the trials available, there is a heavy pharmaceutical industry presence. There are two very large meta-analyses for the safety of naproxen. It is expected that towards the end of 2015 the results from the PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen) trial will be available, with the aim of comparing cardiovascular safety of celecoxib with naproxen or ibuprofen. [9]

Furthermore, studies for naproxen and piroxicam (older NSAIDs) are limited, of poor methodological quality and mostly observational.

Summary:
The available evidence suggests that ibuprofen, meloxicam, naproxen and piroxicam shows comparable efficacy in terms of analgesia.

The FDA has recently included a black box warning for all NSAIDs with regards to cardiovascular side effects and heart failure. Although naproxen appears to be the safest NSAID in this regard, the community appears to be awaiting the results of the PRECISION trial before making a recommendation for the use of naproxen in susceptible patient populations[xxv]. Piroxicam shows a trend towards lower cardiovascular risk, similar to naproxen; whilst limited data suggests a moderate cardiovascular risk associated with meloxicam comparable to ibuprofen.

Meloxicam appears to have few gastrointestinal effects, while being effective for pain relief at both 7.5 mg and 15 mg, with the caveat that these results are heavily influenced by industry. The safety of meloxicam did not appear to be affected by patient demographics (e.g. age, gender)[iv].

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